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☐	L7	L6 and deficiency	10
☐	L6	L5 and PKR	36
☐	L5	HCV adj replicon	346
☐	L4	L3 and PKR	0
☐	L3	L2 and 424/228.1.ICLS.	3
☐	L2	L1 and 435/325.ICLS.	666
☐	L1	435/235.1.ICLS.	3226

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 NEWS  7  MAY 30  IPC 8 Rolled-up Core codes added to CA/CAplus and
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 NEWS  8  MAY 30  The F-Term thesaurus is now available in CA/CAplus
 NEWS  9  JUN 02  The first reclassification of IPC codes now complete in
                  INPADOC
 NEWS 10  JUN 26  TULSA/TULSA2 reloaded and enhanced with new search and
                  and display fields
 NEWS 11  JUN 28  Price changes in full-text patent databases EPFULL and PCTFULL
 NEWS 12  JUl 11  CHEMSAFE reloaded and enhanced
 NEWS 13  JUl 14  FSTA enhanced with Japanese patents
 NEWS 14  JUl 19  Coverage of Research Disclosure reinstated in DWPI
 NEWS 15  AUG 09  INSPEC enhanced with 1898-1968 archive
 NEWS 16  AUG 28  ADISCTI Reloaded and Enhanced
 NEWS 17  AUG 30  CA(SM)/CAplus(SM) Austrian patent law changes
 NEWS 18  SEP 11  CA/CAplus enhanced with more pre-1907 records
 NEWS 19  SEP 21  CA/CAplus fields enhanced with simultaneous left and right
                  truncation
 NEWS 20  SEP 25  CA(SM)/CAplus(SM) display of CA Lexicon enhanced
 NEWS 21  SEP 25  CAS REGISTRY(SM) no longer includes Concord 3D coordinates
 NEWS 22  SEP 25  CAS REGISTRY(SM) updated with amino acid codes for pyrrolysine
 NEWS 23  SEP 28  CEABA-VTB classification code fields reloaded with new
                  classification scheme

 NEWS EXPRESS  JUNE 30 CURRENT WINDOWS VERSION IS V8.01b, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

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=> (HCV sub-genomic)
         11292 HCV
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         11296 HCV
                 (HCV OR HCVS)
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         94797 SUB
                 (SUB OR SUBS)
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         13396 GENOMICS
        117269 GENOMIC
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L1           5 (HCV SUB-GENOMIC)
                 (HCV(W)SUB(W)GENOMIC)

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         11292 HCV
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         11296 HCV
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          3486 REPLICON
          1672 REPLICONS
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L2          443 HCV (S) REPLICON

=> PKR
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            10 PKRS
L3          1612 PKR
                 (PKR OR PKRS)
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=> L3 and L2
L4 13 L3 AND L2

=> D L4 IBIB ABS 1-13

L4 ANSWER 1 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:741350 CAPLUS
DOCUMENT NUMBER: 145:143589
TITLE: Replication of hepatitis C virus (HCV) RNA in mouse embryonic fibroblasts: protein kinase R (PKR)-dependent and PKR-independent mechanisms for controlling HCV RNA replication and mediating interferon activities
AUTHOR(S): Chang, Kyung-Soo; Cai, Zhaohui; Zhang, Chen; Sen, Ganes C.; Williams, Bryan R. G.; Luo, Guangxiang
CORPORATE SOURCE: Department of Microbiology, Immunology, and Molecular Genetics, University of Kentucky College of Medicine, Lexington, KY, 40536-0298, USA
SOURCE: Journal of Virology (2006), 80(15), 7364-7374
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hepatitis C virus (HCV) infection causes chronic hepatitis and is currently treated with α interferon (IFN-α)-based therapies. The underlying mechanisms of chronic HCV infection and IFN-based therapies, however, have not been defined. Protein kinase R (PKR) was implicated in the control of HCV replication and mediation of IFN-induced antiviral response. In this report, the authors demonstrate that a subgenomic RNA replicon of genotype 2a HCV replicated efficiently in mouse embryonic fibroblasts (MEFs), as determined by cell colony formation efficiency and the detection of HCV proteins and both pos.- and neg.-strand RNAs. Addnl., the subgenomic HCV RNA was found to replicate more efficiently in the PKR knockout (PKR-/-) MEF than in the wild-type (PKR+/+) MEF. The knockdown expression of PKR by specific small interfering RNAs significantly enhanced the level of HCV RNA replication, suggesting that PKR is involved in the control of HCV RNA replication. The level of ISG56 (p56) was induced by HCV RNA replication, indicating the activation of PKR-independent antiviral pathways. Furthermore, IFN-α/β inhibited HCV RNA replication in PKR-/- MEFs as efficiently as in PKR+/+ MEFs. These findings demonstrate that PKR-independent antiviral pathways play important roles in controlling HCV replication and mediating IFN-induced antiviral effect. These findings also provide a foundation for the development of transgenic mouse models of HCV replication and set a stage to further define the roles of cellular genes in the establishment of chronic HCV infection and the mediation of intracellular innate antiviral response by using MEFs derived from diverse gene knockout animals.
REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:687956 CAPLUS
TITLE: Investigating the inhibitory effects of interferon-α on the replication of hepatitis C virus replicon
AUTHOR(S): Jia, Yintang; Wei, Lai; Jiang, Dong; Cong, Xu; Fei, Ran
CORPORATE SOURCE: People's Hospital, Peking University, Beijing, 100044, Peop. Rep. China
SOURCE: Zhonghua Yixue Zazhi (Beijing, China) (2005), 85(29), 2065-2069

CODEN: CHHTAT; ISSN: 0376-2491
PUBLISHER: Zhonghua Yixuehui Zazhishe
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB The inhibitory effects of interferon-α (IFN-α) on HCV replicon were investigated to evaluate the expressing levels of signal transducer and activator of transcription genes (STAT1 and STAT2) and IFN-α stimulated genes (ISGs) which may mediate the inhibitory effects of IFN-α on HCV. Firstly HCV replicon cell culture system was established by transfecting HCV replicon RNA transcribed in vitro into Huh7 cells and screening with G418. Secondly, the established HCV replicon cells were treated with various concns. of IFN-α (0, 10, 25, 50, 100, 250, 500, 750, 1000, 2500, and 5000 IU/mL) for 72 h or treated with 1000 IU/mL of IFN-α for different lengths of time (0, 24, 48, 72, 96 h), then the levels of HCV RNA and NS5A protein in these cells were examined by semi-quant. RT-PCR and Western blot resp. IFN-α could effectively inhibit HCV RNA replication. The 10 IU/mL or 25 IU/mL of IFN-α could lead to about 68% and 75% of HCV-RNA reduction resp. The cells treated with 1000 IU/mL IFN-α for 24 h or 96 h had about 75% and 88% of HCV RNA reduction compared with the cells of control, demonstrated that the inhibitory effects of IFN-α on HCV replicon were in dose and time dependent manners. The expressions of antiviral ISGs-PKR, 2'5'OAS, G1P3, ISG20 and ISGF3γ were strongly induced by IFN-α. HCV replicons were sensitive to IFN-α treatment. The inhibitory effects of IFN-α on HCV RNA and NS5A were both dose and time dependent. PKR, 2'5'OAS, G1P3, ISG20 and ISGF3γ might mediate the inhibitory effects of IFN-α on HCV replicon replication.

L4 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:197890 CAPLUS
TITLE: Cloning and expression of double-stranded RNA activated protein kinase (PKR) and its effect on hepatitis C virus internal ribosome entry site (IRES) directed protein synthesis
AUTHOR(S): Jia, Yin-Tang; Wei, Lai; Jiang, Dong; Cong, Xu; Fei, Ran
CORPORATE SOURCE: Institute of Hepatology, Peking University People's Hospital, Beijing, 100044, Peop. Rep. China
SOURCE: Zhongguo Shengwu Huaxue Yu Fenzi Shengwu Xuebao (2006), 22(1), 24-30
CODEN: ZSHXF2; ISSN: 1007-7626
PUBLISHER: Zhongguo Shengwu Huaxue Yu Fenzi Shengwu Xuebao Bianjibu
DOCUMENT TYPE: Journal
LANGUAGE: Chinese

AB Interferon-α (IFN-α) based therapy is a major strategy to copy with hepatitis C virus (HCV) infection. But there is still a part of patients who could not obtain sustained virol. response (SRV) after treated with IFN-α due to the resistance of HCV to IFN-α. One of the explanation is that the NS5A and E2 proteins coded by HCV counteract the double-stranded RNA activated protein kinase (PKR) activity which can lead to viral protein synthesis shutoff. But whether or not PKR play a role in the inhibition of HCV IRES directed viral protein synthesis has the controversial reports currently. To clarify the debate, it was firstly confirmed by Western blotting that IFN-α treatment led to the increased expression of PKR and eIF2α-P proteins, but inhibitions of NS5A and NPT II proteins expression, which were in a dose-dependent manner. Thereafter, the wild type PKR expression vector(pPKRwt) and mutated PKR expression vector(pPKRΔ6) which contained a deletion of 6 amino acids in the kinase domain and thus has the dominant neg. regulatory

function were constructed, then pPKRwt /pPKRΔ6 were cotransfected with HCV replicon RNA into Huh7 cells. The levels of NPT II protein directed by HCV IRES were detected by immunoblot and compared with that of the cells transfected with empty vector and the cells treated with IFN-α along. The results showed that NPT II protein level in the cells transfected with pPKRwt was lower than that of the cells transfected with empty vector but higher than that of the cells treated with IFN-α. Whereas, the level of NPT II protein in the cells transfected with pPKRΔ6 was no significant different from that of the cells transfected with empty vector, but expression of PKR Δ6 could partially rescue the NPT II protein synthesis from the inhibition of IFN-α. In conclusion, the results indicated that PKR partially mediated the inhibitory effects of IFN-α on HCV IRES directed viral protein synthesis, but other PKR -independent mechanism might also be involved in the inhibitory effect of IFN-α on viral protein synthesis.

L4 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:92034 CAPLUS
DOCUMENT NUMBER: 145:5445
TITLE: Mechanistic link between the anti-HCV effects of interferon gamma control of viral replication by a Ras-MAPK signaling cascade
AUTHOR(S): Huang, Ying; Chen, Xinyi Cynthia; Konduri, Madhavi; Fomina, Nadejda; Lu, Jin; Jin, Ling; Kolykhalov, Alexander; Tan, Seng-Lai
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA
SOURCE: Hepatology (Hoboken, NJ, United States) (2005), Volume Date 2006, 43(1), 81-90
CODEN: HPTLD9; ISSN: 0270-9139
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Interferon-gamma (IFN-γ) exerts potent antiviral activity in the hepatitis C virus (HCV) replicon systems. However, the mechanisms underlying the direct antiviral effect have not been determined We found that the type II transcriptional response to IFN-γ could be suppressed by inhibition of MEK1/2 kinase activity by MEK1/2 inhibitor U0126 in the hepatoma cell line Huh-7. Using a bicistronic HCV replicon system expressing a luciferase reporter gene in Huh-7 cells (RLuc-replicon), we showed that inhibition of MEK1/2 kinase activity is sufficient to counteract the antiviral activity of IFN-γ. Expression of a constitutive active form of Ras inhibited the luciferase activity of RLuc-replicon, whereas a dominant-neg. mutant of Ras enhanced the reporter activity, indicating that the Ras-MAPK pathway has a role in limiting replication of the viral RNA. Consistent with the involvement of the Ras-MAPK pathway, treatment with epidermal growth factor suppressed HCV protein expression in the RLuc-replicon cells, an effect that could be abolished by U0126. Inhibition of MEK1/2 kinase activity correlated with reduced phosphorylation of the HCV NS5A protein and enhanced RLuc-replicon luciferase reporter activity, in line with recent reports that phosphorylation of NS5A neg. modulates HCV RNA replication. Finally, genetic deletion anal. in yeast supported the role of a MEK-like kinase(s) in the regulation of NS5A phosphorylation. In conclusion, the direct anti-HCV effect of IFN-γ in cell culture is, at least in part, mediated through the Ras-MAPK signaling pathway, which possibly involves a direct or indirect modulation of NS5A protein phosphorylation.
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1028069 CAPLUS

DOCUMENT NUMBER: 143:311927
TITLE: RNA interference-mediated inhibition of hepatitis C virus infection/replication using multifunctional short interfering nucleic acid (siNA) targeting viral or cellular RNA
INVENTOR(S): Jadhav; Vasant; Kossen, Karl; Zinnen, Shawn; Vaish, Narendra; Mcswiggen, James
PATENT ASSIGNEE(S): Sirna Therapeutics, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 176 pp., Cont.-in-part of Appl. No. PCT/US04/016390.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 242
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005209180	A1	20050922	US 2004-942560	20040915
AU 9851819	A1	19980611	AU 1998-51819	19980112
AU 729657	B2	20010208		
AU 9939188	A1	19990916	AU 1999-39188	19990713
AU 769175	B2	20040115	AU 2000-56616	20000911
WO 2002081494	A1	20021017	WO 2002-US9187	20020326
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US 2005-703946P	P	20050729
US 2005-737024P	P	20051115

AB This invention relates to compds., compns., and methods useful for inhibiting hepatitis C virus (HCV) infection or replication by RNA interference using multifunctional short interfering nucleic acid (siNA) mols. The multifunctional siNA's comprise three oligonucleotides, the first oligonucleotide of which is complementary to the two other oligonucleotides. The first oligonucleotide consists of nucleic acid complementary to the second oligonucleotide linked by a nucleotide or non-nucleotide linker to nucleic acid complementary to the third oligonucleotide. Thus, the multifunctional siNA gives rise to two siNA mols., each of which targets a different portion of the HCV RNA, upon cleavage by the RISC complex. Alternatively, one or both of the resulting siNA mols. could target cellular RNA sequences encoding protein required for HCV infection or replication, e.g., La antigen, FAS, FAS ligand, interferon regulatory factor, PKR protein, eIF2Bγ, eIF2γ, DEAD box protein DDX3, or polypyrimidine tract-binding protein. Thus, a multifunctional siNA targeting two different sites on HCV RNA was as efficient as two sep. siNA's targeting these same two sites in inhibiting HCV replication in an HCV replicon system in Huh7 cells.

L4 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:421181 CAPLUS
DOCUMENT NUMBER: 142:480641
TITLE: New antiviral pathway that mediates hepatitis C virus replicon interferon sensitivity through ADAR1
AUTHOR(S): Taylor, Deborah R.; Puig, Montserrat; Darnell, Miriam E. R.; Mihalik, Kathleen; Feinstone, Stephen M.
CORPORATE SOURCE: Laboratory of Hepatitis Viruses, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD, 20892, USA
SOURCE: Journal of Virology (2005), 79(10), 6291-6298
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB While many clin. hepatitis C virus (HCV) infections are resistant to alpha interferon (IFN-α) therapy, subgenomic in vitro

self-replicating HCV RNAs (HCV replicons) are characterized by marked IFN-α sensitivity. IFN-α treatment of replicon-containing cells results in a rapid loss of viral RNA via translation inhibition through double-stranded RNA-activated protein kinase (PKR) and also through a new pathway involving RNA editing by an adenosine deaminase that acts on double-stranded RNA (ADAR1). More than 200 genes are induced by IFN-α, and yet only a few are attributed with an antiviral role. We show that inhibition of both PKR and ADAR1 by the addition of adenovirus-associated RNA stimulates replicon expression and reduces the amount of inosine recovered from RNA in replicon cells. Small inhibitory RNA, specific for ADAR1, stimulated the replicon 40-fold, indicating that ADAR1 has a role in limiting replication of the viral RNA. This is the first report of ADAR's involvement in a potent antiviral pathway and its action to specifically eliminate HCV RNA through adenosine to inosine editing. These results may explain successful HCV replicon clearance by IFN-α in vitro and may provide a promising new therapeutic strategy for HCV as well as other viral infections.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:624602 CAPLUS

DOCUMENT NUMBER: 142:108935

TITLE: Purification and characterization of hepatitis C virus non-structural protein 5A expressed in Escherichia coli

AUTHOR(S): Huang, Luyun; Sineva, Elena V.; Hargittai, Michele R. S.; Sharma, Suresh D.; Suthar, Mehul; Raney, Kevin D.; Cameron, Craig E.

CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Pennsylvania State University, University Park, PA, 16802, USA

SOURCE: Protein Expression and Purification (2004), 37(1), 144-153
CODEN: PEXPEJ; ISSN: 1046-5928

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have employed a pET-ubiquitin expression system to produce two his-tagged forms of hepatitis C virus (HCV) non-structural protein 5A (NS5A) in Escherichia coli. One derivative contains the full-length protein extended to include a carboxy-terminal hexahistidine tag; the other derivative contains an amino-terminal hexahistidine tag in place of the 32 amino acid amphipathic helix that mediates membrane association At least 1 mg of each derivative at a purity of 90% could be produced from a 1-L culture. The purified derivs. produced high titer antibody that recognized both p56 and p58 forms of NS5A in Huh-7.5 cells expressing an HCV subgenomic replicon. The NS5A derivs. were efficiently phosphorylated by casein kinase II, leading to at least 5 mol of phosphate incorporated per mol of protein. Interestingly, this level of phosphorylation did not alter the migration of the protein in an SDS-polyacrylamide gel, suggesting that hyperphosphorylation alone is not sufficient to generate the p58 form of NS5A observed in Huh-7 cells. Neither NS5A derivative was capable of inhibiting the eIF2α-phosphorylation activity of the activated form of the double-stranded RNA-activated protein kinase, PKR, suggesting that NS5A phosphorylation may be required for this function of NS5A. However, both unphosphorylated derivs. were shown to interact with NS5B, the HCV RNA-dependent RNA polymerase, in solution by using a novel kinase-protection assay. The availability of purified HCV NS5A will permit rigorous biochem. and biophys. characterization of this protein, ultimately providing insight into the function of this protein during HCV genome replication.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:299580 CAPLUS
DOCUMENT NUMBER: 140:390125
TITLE: Hepatitis C virus NS5A protein interacts with 2',5'-oligoadenylate synthetase and inhibits antiviral activity of IFN in an IFN sensitivity-determining region-independent manner
AUTHOR(S): Taguchi, Takashi; Nagano-Fujii, Motoko; Akutsu, Masato; Kadoya, Hiroyasu; Ohgimoto, Shinji; Ishido, Satoshi; Hotta, Hak
CORPORATE SOURCE: Division of Microbiology, Division of Diabetes, Digestive and Kidney Diseases, Kobe University Graduate School of Medicine, Kobe, 650-0017, Japan
SOURCE: Journal of General Virology (2004), 85(4), 959-969
CODEN: JGVIAY; ISSN: 0022-1317
PUBLISHER: Society for General Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The non-structural protein 5A (NS5A) of hepatitis C virus (HCV) has been implicated in inhibition of antiviral activity of IFN. While previous studies have suggested an interaction between NS5A and the double-stranded RNA-dependent protein kinase (PKR), the possibility still remains that interaction with another mol.(s) is involved in the NS5A-mediated inhibition of IFN. In the present study, the authors investigated a possible interaction between NS5A and 2',5'-oligoadenylate synthetase (2-5AS), another key mol. in antiviral activity. The authors observed that NS5A phys. interacted with 2-5AS in cultured cells, with an N-terminal portion of NS5A [aa 1-148; NS5A(1-148)] and two sep. portions of 2-5AS (aa 52-104 and 184-275) being involved in the interaction. Single point mutations at residue 37 of NS5A affected the degree of the interaction with 2-5AS, with a Phe-to-Leu mutation (F37L) augmenting and a Phe-to-Asn mutation (F37N) diminishing it. Virus rescue assay revealed that the full-length NS5A (NS5A-F) and NS5A(1-148), the latter of which contains neither the IFN sensitivity-determining region (ISDR) nor the PKR-binding domain, significantly counteracted the antiviral activity of IFN. Introduction of a F37N mutation into NS5A(1-148) impaired the otherwise more significant IFN-inhibitory activity of NS5A(1-148). It was also found that the F37N mutation was highly disadvantageous for the replication of an HCV RNA replicon. Taken together, the results suggest the possibility that NS5A interacts with 2-5AS and inhibits the antiviral activity of IFN in an ISDR-independent manner.
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:246783 CAPLUS
DOCUMENT NUMBER: 138:253417
TITLE: Alpha interferon induces distinct translational control programs to suppress hepatitis C virus RNA replication
AUTHOR(S): Wang, Chunfu; Pflugheber, Jill; Sumpter, Rhea, Jr.; Sodora, Donald L.; Hui, Daniel; Sen, Ganes C.; Gale, Michael, Jr.
CORPORATE SOURCE: Department of Microbiology, University of Texas Southwestern Medical Center, Dallas, TX, 75390, USA
SOURCE: Journal of Virology (2003), 77(7), 3898-3912
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hepatitis C virus (HCV) infection is treated with interferon (IFN)-based

therapy. The mechanisms by which IFN suppresses HCV replication are not known, and only limited efficacy is achieved with therapy because the virus directs mechanisms to resist the host IFN response. In the present study we characterized the effects of IFN action upon the replication of two distinct quasispecies of an HCV replicon whose encoded NS5A protein exhibited differential abilities to bind and inhibit protein kinase R (PKR). Metabolic labeling expts. revealed that IFN had little overall effect upon HCV protein stability or polyprotein processing but specifically blocked translation of the HCV RNA, such that the replication of both viral quasispecies was suppressed by IFN treatment of the Huh7 host cells. However, within cells expressing an NS5A variant that inhibited PKR, we observed a reduced level of eukaryotic initiation factor 2 alpha subunit (eIF2α) phosphorylation and a concomitant increase in HCV protein synthetic rates, enhancement of viral RNA replication, and a partial rescue of viral internal ribosome entry site (IRES) function from IFN suppression. Assessment of the ribosome distribution of the HCV replicon RNA demonstrated that the NS5A-mediated block in eIF2α phosphorylation resulted in enhanced recruitment of the HCV RNA into polyribosome complexes in vivo but only partially rescued the RNA from polyribosome dissociation induced by IFN treatment. Examination of cellular proteins associated with HCV-translation complexes in IFN-treated cells identified the P56 protein as an eIF3-associated factor that fractionated with the initiator ribosome-HCV RNA complex. Importantly, we found that P56 could independently suppress HCV IRES function both in vitro and in vivo, but a mutant P56 that was unable to bind eIF3 had no suppressive action. We conclude that IFN blocks HCV replication through translational control programs involving PKR and P56 to, resp., target eIF2- and eIF3-dependent steps in the viral RNA translation initiation process.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:839576 CAPLUS

DOCUMENT NUMBER: 138:151291

TITLE: Endoplasmic reticulum (ER) stress: hepatitis C virus induces an ER-nucleus signal transduction pathway and activates NF-κB and STAT-3

AUTHOR(S): Waris, Gulam; Tardif, Keith D.; Siddiqui, Aleem

CORPORATE SOURCE: Program in Molecular Biology, Department of Microbiology, University of Colorado Health Sciences Center, Denver, CO, 80262, USA

SOURCE: Biochemical Pharmacology (2002), 64(10), 1425-1430
CODEN: BCPCA6; ISSN: 0006-2952

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Human hepatitis C virus (HCV) is the leading cause of chronic hepatitis, which often results in liver cirrhosis and hepatocellular carcinoma. The HCV RNA genome codes for at least ten proteins. The HCV non-structural protein 5A (NS5A) has generated considerable interest due to its effect on interferon sensitivity via binding and inactivating the cellular protein kinase, PKR. It has been shown that NS5A engages in the endoplasmic reticulum (ER)-nucleus signal transduction pathway. The expression of NS5A in the ER induces an ER stress ultimately leading to the activation of STAT-3 and NF-κB. This pathway is sensitive to inhibitors of Ca2+ uptake in the mitochondria (ruthenium red), Ca2+ chelators (TMB-8, EGTA-AM), and antioxidants (PDTC, NAC, Mn-SOD). The inhibitory effect of protein tyrosine kinase (PTK) inhibitors indicates the involvement of PTK in NF-κB activation by NS5A. This implicates an alternate pathway of NF-κB activation by NS5A. The actions of NS5A have also been studied in the context of an HCV subgenomic replicon inducing a similar intracellular event. Thus, activation of NF-κB leads to the induction of cellular genes, which are largely

antiapoptotic in function. These studies suggest a potential function of NS5A in inducing chronic liver disease and hepatocellular carcinoma associated with HCV infection.
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:795990 CAPLUS
DOCUMENT NUMBER: 138:101867
TITLE: PKR-dependent mechanisms of gene expression from a subgenomic hepatitis C virus clone
AUTHOR(S): Rivas-Estilla, Ana Maria; Svitkin, Yuri; Lastra, Marcelo Lopez; Hatzoglou, Maria; Sherker, Averell; Koromilas, Antonis E.
CORPORATE SOURCE: Lady Davis Institute for Medical Research, Sir Mortimer B. Davis-Jewish General Hospital, McGill University, Montreal, QC, H3T 1E2, Can.
SOURCE: Journal of Virology (2002), 76(21), 10637-10653
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Studies on hepatitis C virus (HCV) replication have been greatly advanced by the development of cell culture models for HCV known as replicon systems. The prototype replicon consists of a subgenomic HCV RNA in which the HCV structural region is replaced by the neomycin phosphotransferase II (NPTII) gene, and translation of the HCV proteins NS3 to NS5 is directed by the encephalomyocarditis virus (EMCV) internal ribosome entry site (IRES). The interferon (IFN)-inducible protein kinase PKR plays an important role in cell defense against virus infection by impairing protein synthesis as a result of eIF-2α phosphorylation. Here, we show that expression of the viral nonstructural (NS) and PKR proteins and eIF-2α phosphorylation are all variably regulated in proliferating replicon Huh7 cells. In proliferating cells, induction of PKR protein by IFN-α is inversely proportional to viral RNA replication and NS protein expression, whereas eIF-2α phosphorylation is induced by IFN-α in proliferating but not in serum-starved replicon cells. The role of PKR and eIF-2α phosphorylation was further addressed in transient-expression assays in Huh7 cells. These expts. demonstrated that activation of PKR results in the inhibition of EMCV IRES-driven NS protein synthesis from the subgenomic viral clone through mechanisms that are independent of eIF-2α phosphorylation. Unlike NS proteins, HCV IRES-driven NPTII protein synthesis from the subgenomic clone was resistant to PKR activation. Interestingly, activation of PKR could induce HCV IRES-dependent mRNA translation from dicistronic constructs, but this stimulatory effect was mitigated by the presence of the viral 3' untranslated region. Thus, PKR may assume multiple roles in modulating HCV replication and protein synthesis, and tight control of PKR activity may play an important role in maintaining virus replication and allowing infection to evade the host's IFN system.
REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:290303 CAPLUS
DOCUMENT NUMBER: 137:151014
TITLE: Regulation of PKR and IRF-1 during hepatitis C virus RNA replication
AUTHOR(S): Pflugheber, Jill; Fredericksen, Brenda; Sumpter, Rhea, Jr.; Wang, Chunfu; Ware, Felecia; Sodora, Donald L.; Gale, Michael, Jr.
CORPORATE SOURCE: Department of Microbiology, University of Texas

Southwestern Medical Center, Dallas, TX, 75390-9048, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2002), 99(7), 4650-4655
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The virus-host interactions that influence hepatitis C virus (HCV) replication are largely unknown but are thought to involve those that disrupt components of the innate intracellular antiviral response. Here we examined cellular antiviral pathways that are triggered during HCV RNA replication. We report that (i) RNA replication of HCV subgenomic replicons stimulated double-stranded RNA (dsRNA) signaling pathways within cultured human hepatoma cells, and (ii) viral RNA replication efficiency corresponded with an ability to block a key cellular antiviral effector pathway that is triggered by dsRNA and includes IFN regulatory factor-1 (IRF-1) and protein kinase R (PKR). The block to dsRNA signaling was mapped to the viral nonstructural 5A (NS5A) protein, which colocalized with PKR and suppressed the dsRNA activation of PKR during HCV RNA replication. NS5A alone was sufficient to block both the activation of IRF-1 and the induction of an IRF-1-dependent cellular promoter by dsRNA. Mutations that clustered in or adjacent to the PKR-binding domain of NS5A relieved the blockade to this IRF-1 regulatory pathway, resulting in induction of IRF-1-dependent antiviral effector genes and the concomitant reduction in HCV RNA replication efficiency. Our results provide further evidence to support a role for PKR in dsRNA signaling processes that activate IRF-1 during virus infection and suggest that NS5A may influence HCV persistence by blocking IRF-1 activation and disrupting a host antiviral pathway that plays a role in suppressing virus replication.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:123200 CAPLUS
DOCUMENT NUMBER: 136:178940
TITLE: Cells with enhanced replication of hepatitis C virus sub-genomic RNA and its use in antiviral drug screening
INVENTOR(S): Lu, Hui-Hua; Selby, Mark
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002012477	A2	20020214	WO 2001-US124276	20010803
WO 2002012477	A3	20030410		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2416633	AA	20020214	CA 2001-2416633	20010803
AU 2001078139	A5	20020218	AU 2001-78139	20010803

US 2002142455	A1	20021003	US 2001-922962	20010803
US 6660471	B2	20031209		
EP 1320583	A2	20030625	EP 2001-956106	20010803
EP 1320583	B1	20060301		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
AT 318893	E	20060315	AT 2001-956106	20010803
US 2004076612	A1	20040422	US 2003-684846	20031014
PRIORITY APPLN. INFO.:			US 2000-223244P	P 20000804
			US 2001-922962	A3 20010803
			WO 2001-US24276	W 20010803

AB This invention provides methods for generating cells that stably replicate sub-genomic virus replicons. This invention also provides methods of generating cells that have disabled PKR (a cellular ds-RNA-dependent protein kinase) activity and that stably replicate HCV subgenomic replicons. Specifically, HCV subgenomic E2 replicon-transfected Huh-7 cells are established by blocking PKR activity through over-expressing PKR dominant-neg. mutant [Arg296] (in which the PKR active site Lys296 is mutated to Arg296). Addnl., the PKR activity is disabled by co-expressing recombinant p58IPK, a PKR inhibitor, and antisense PKR DNA in the presence of 5-amino purine. The invention also provides methods of using the cells of the invention to screen for compds. that modulate other viral RNA replication, including HCV RNA replication.